Case Report

Effect of intravesical botulinum toxin injection on symptoms of autonomic dysreflexia in a patient with chronic spinal cord injury: a case report

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Context: There are few treatment options for managing autonomic dysreflexia in patients with chronic spinal cord injury (SCI). According to some studies, intravesical botulinum toxin for SCI patients with autonomic dysreflexia has a preventive effect on symptoms of autonomic dysreflexia. However, the usefulness of an intravesical botulinum toxin injection has never been reported for autonomic dysreflexia in an adult patient with chronic cervical SCI, although there has been for one pediatric patient.

Findings: A 62-year-old man with chronic cervical SCI had neurogenic bladder due to C6-7 SCI since sustaining a fall in 1980. He presented with an intermittent headache and severe hypertension because of persistent autonomic dysreflexia. His symptoms did not improve with conservative management, and he could not undergo an operation to resect the lung cancer because of his uncontrolled blood pressure. To control his fluctuating blood pressure, he was taken to an operating room to receive an intravesical botulinum toxin injection for refractory bladder spasms. Subsequently, his blood pressure was controlled, and then the lung mass could be surgically removed. His improved condition lasted for more than 6 months.

Conclusion: This case suggests that botulinum toxin is a logical treatment option for autonomic dysreflexia as well as neurogenic detrusor overactivity in patients with chronic SCI. Dedicated research is warranted to assess the efficacy of an intravesical botulinum toxin injection, as it was used successfully to stop the symptoms of autonomic dysreflexia in our patient.

Keywords: Autonomic dysreflexia, Hypertension, Botulinum toxins, Spinal cord injuries, botox

Introduction

A patient with chronic cervical spinal cord injury (SCI) can have many complications, such as respiratory dysfunction, cardiovascular problems, bladder/bowel dysfunction, spasticity, and pain.[1] Autonomic dysreflexia, a cardiovascular complication, is one of the most life-threatening complications secondary to SCI at the T6 level or higher.[2] Many symptoms of autonomic dysreflexia develop due to various stimuli, such as paroxysmal hypertension, bradycardia, headaches, etc. The health care cost burden in patients with SCI with autonomic dysreflexia is high, and effective treatment methods are insufficient.[3]

An intravesical botulinum toxin injection, which has a reversible effect and few serious side effects, is used in patients with SCI who experience urinary incontinence. According to some research studies,[4,5] an intravesical botulinum toxin has a preventive effect on autonomic dysreflexia in patients with SCI. After an intravesical botulinum injection, the symptoms of autonomic dysreflexia improved for more than 6 months in one pediatric patient with SCI.[6] However, patients with low bladder compliance may not experience any advantage from a botulinum toxin injection because of possible bladder muscle changes, such as fibrosis, which are more

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common in people with chronic SCI.[4] Furthermore, there are no reports of using botulinum toxin in an adult with chronic SCI with autonomic dysreflexia. Here, we describe a patient living with chronic SCI for more than 35 years, in whom an intravesical botulinum toxin was used to treat persistent autonomic dysreflexia.

Case report

A 62-year-old male with chronic cervical SCI who visited the rehabilitation medicine outpatient clinic in February 2016 had voiding dysfunction due to C6-7 SCI since he sustained a fall in 1980, and he had undergone a C6 and C7 vertebrae fusion (posterior approach) operation. Postoperatively, he had been in a quadriplegic state with neurogenic bladder for more than 35 years. According to the institutional review board's guidelines, the patient's consent was obtained to publish his case anonymously.

He reported intermittent symptoms of a headache, dyspnea, and palpitation at dawn, which developed 5 years ago. His systolic blood pressure at home was observed as high as 180 mmHg with these symptoms. There were no abnormal findings in terms of electrocardiography, cardiac biomarkers, and coronary computed tomography. The size of the cardiac chambers and left ventricular systolic function were generally normal (ejection fraction 74%) on a transthoracic echocardiogram. During 24-hour blood pressure monitoring, his systolic blood pressure fluctuated from 80 mmHg to 150 mmHg. Dyspnea was not related to the blood pressure change, and it was not induced by decreasing his oxygen saturation. In addition, the findings of polysomnography were not specific. Constipation and infection were excluded from the causes of these symptoms, and he was managed with oral antihypertensive medications. Since intermittent increases in paroxysmal blood pressure and headache persisted, we concluded that these symptoms were caused by autonomic dysreflexia.

The patient had initially used a clean intermittent catheterization regimen for bladder management. However, there was no caregiver available to help with his voiding and care. Consequentially, a suprapubic catheter was inserted into his bladder for long-term care, because he had recurrent urinary tract infections and epididymitis caused by an indwelling urethral catheter. As bladder distension can be one of the causes of autonomic dysreflexia, despite the patients taking an α-blocker (alfuzosin) and anticholinergics (solifenacin), a urodynamic study was performed 1 month after the outpatient visit. Neurogenic detrusor overactivity was confirmed at the terminal phase. The bladder capacity and detrusor pressure at the maximum cystometric capacity were 420 mL and 34 cmH_2O, respectively, meaning that the detrusor pressure was not high, and the bladder had a normal volume (Fig. 1).

The patient had underlying diseases such as diabetes mellitus, hypertension, and bilateral adrenal masses that were discovered to be tumors were found incidentally without clinical symptoms or signs. The abdominal computed tomography scan showed that the adrenal masses were non-functioning, and results of the hormonal evaluation indicated acute pyelonephritis. During the cardiac examination, a solitary pulmonary mass was detected, but the operation for mass removal could not be performed because of his unstable blood pressure. The patient received an intravesical botulinum toxin injection to control the symptoms of autonomic dysreflexia 1 week after the urodynamic study. Botox® (Allergan Inc., Irvine, CA, USA) was evenly injected into 30 places of the bladder wall, except for the trigone (200 units), by one qualified urologist.

After 1 month, his blood pressure stabilized, and the daily peak systolic blood pressure decreased to less than 150 mmHg. Because of this, the lung mass (adenocarcinoma, T1aN0M0 stage IA) could be removed by performing a video-assisted thoracoscopic operation. Since atrial fibrillation with a rapid ventricular rate occurred postoperatively, clopidogrel was added to his medication regimen. His symptoms of autonomic dysreflexia and bladder spasms improved for more than 6 months.

Discussion

Subsequent to SCI, the descending central modulation of bladder activity becomes disrupted. However, as spinal bladder reflexes re-emerge several weeks to months after SCI,[7] independent sacral reflex activity leads to uninhibited bladder muscle activation during filling at a given volume threshold and urinary incontinence without the sensation of bladder filling or the urge to void.[8] In addition, the lack of voluntary external sphincter control, unexpected bladder spasm, and uncoordinated activity between the bladder and external sphincter are more common in people with SCI than in others with voiding problems.[8] Among the chronic complications of patients with SCI, one of the most important ones is the loss of genitourinary and gastrointestinal function.[1] When the symptoms of autonomic dysreflexia develop due to neurogenic bowel and bladder, irritation caused by bladder distension can be the most common cause.[9] Even if a patient takes an anti-cholinergic drug, bladder compliance gradually decreases according to the change in muscle cells that line the bladder walls. A change in the bladder can cause even a small amount of urine to induce a vesical pressure increase, and the increased vesical pressure can lead to increased

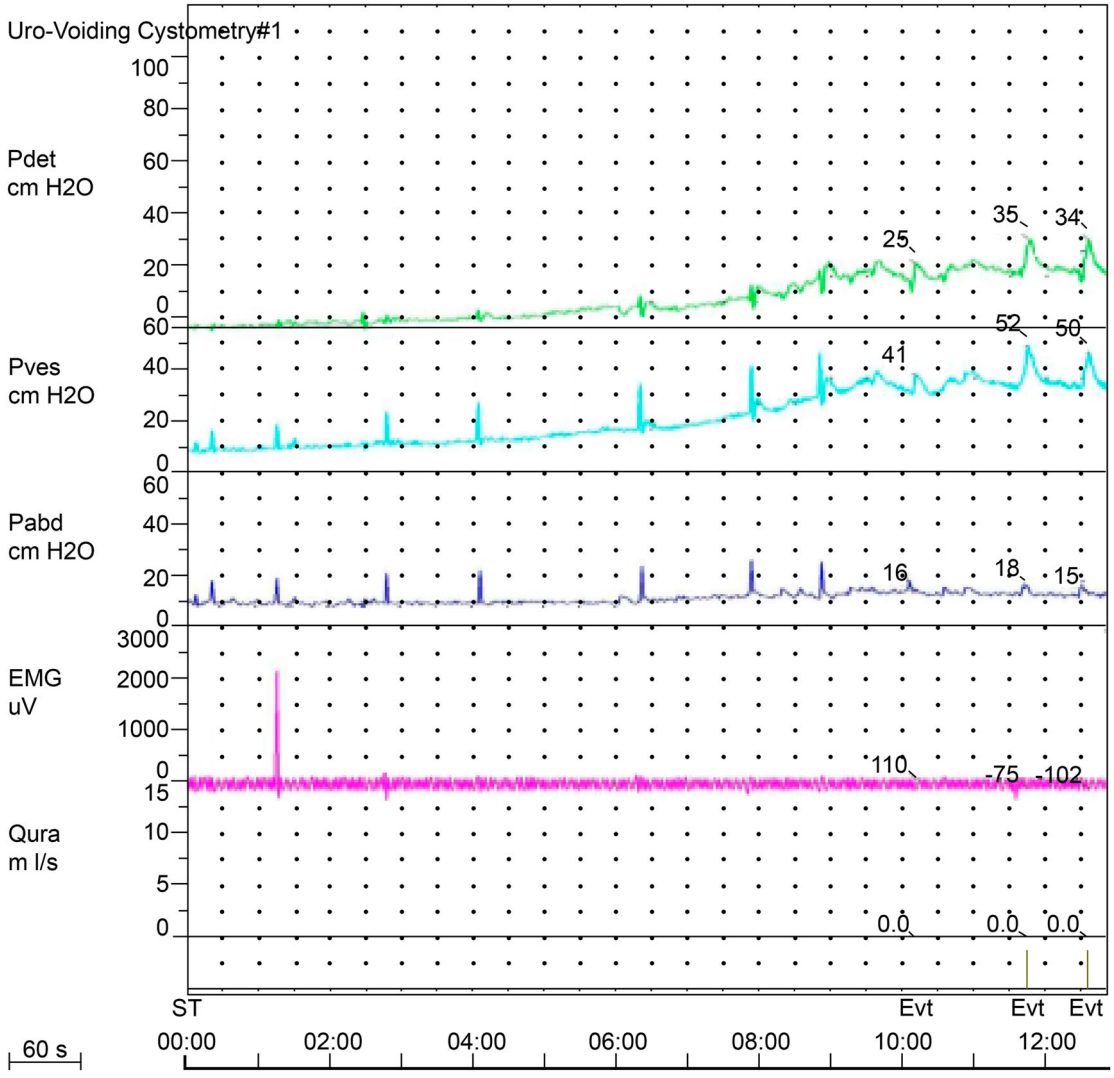

Figure 1 Graph of the urodynamic study before intravesical botulinum toxin injection. Abbreviations: Pdet, detrusor pressure; Pves, intravesical pressure; Pabd, abdominal pressure; EMG, electromyography; Qura, urinary flow rate; ST, start; Evt, overactive event

sympathetic tone. In other words, the symptoms of autonomic dysreflexia can be induced by little irritation, although detrusor pressure is well controlled by regular clean intermittent catheterization.

Nerves innervating a bladder are remodeled, and afferent C-fibers regenerate after SCI. C-fibers have a high threshold to respond to increased bladder pressure, but their activity can be increased by chemical irritation of the bladder mucosa.[10] Therefore, botulinum toxin modulates the afferent C-fibers by decreasing nerve growth factors and inhibiting adenosine triphosphate release in the bladder.[11,12] Furthermore, various changes in the urinary tract occur over time after SCI. When neurogenic bladder develops and becomes chronic, the intravesical tissues undergo fibrotic change, and bladder compliance decreases. An intravesical botulinum toxin injection can decrease such changes. Compared to patients with neurogenic overactive bladder who did not receive an injection of botulinum toxin, those who did receive a botulinum toxin injection showed less fibrosis of the bladder wall in a previous study.[13] As a result, an injection of botulinum toxin into the bladder reduces chemical irritation and mechanical stiffness, thereby increasing bladder compliance.

In the present case, mechanical irritation caused autonomic dysreflexia, because the patient had a suprapubic catheter for urination for a long time. The bladder capacity was within normal range, and bladder compliance was not too high (normal range 12.5–30 mL/cmH_2O) in the urodynamic study.[14] Common effects of injecting the detrusor with botulinum toxin are suppression of bladder overactivity, increase in cystometric and maximum bladder capacity, decrease in voiding pressure, and elimination of urinary incontinence that may be associated with detrusor overactivity.[15] However, the purpose of an intravesical botulinum

toxin injection in this case was to reduce the symptoms of autonomic dysreflexia rather than to control neurogenic detrusor overactivity. The intravesical botulinum toxin injection in our patient who had mild neurogenic detrusor overactivity was used to decrease detrusor muscle spasm and mechanical irritation. As a result, his uncontrolled blood pressure and headache significantly improved, and the underlying lung cancer could be resected. Additionally, improvement in the symptoms of autonomic dysreflexia lasted for more than 6 months. Despite chronic changes in the detrusor muscles and bladder tissues, this case demonstrates that botulinum toxin can decrease the symptoms of autonomic dysreflexia as well as neurogenic detrusor overactivity by decreasing chemical and mechanical irritants.

Among the drugs used to treat overactive bladder, Myrbetriq (mirabegron), which activates the β3 adrenergic receptor in the bladder detrusor muscle, leads to muscle relaxation and an increase in bladder capacity.[16] Myrbetriq, which reduces bladder spasm, may help improve symptoms of autonomic dysreflexia, although the effect of this drug has not been demonstrated in patients with chronic SCI. In addition, surgical treatment, such as bladder augmentation or urostomy, can be used as secondary treatment options. Augmentation cystoplasty has a proven long-term success based on urodynamic studies, and it has been found to decrease the symptoms of autonomic dysreflexia.[17] However, surgical procedures lead to irreversible structural changes and can induce many complications, such as perforation, small bowel obstruction, peristomal skin problems, etc. Thus, when symptoms of autonomic dysreflexia do not improve with medication, an intravesical botulinum toxin injection can be administered as an effective treatment before surgical procedures in patients with chronic SCI.

Conclusions

The common pathways and recent data in the aforementioned discussion suggest that botulinum toxin is a logical treatment option for neurogenic detrusor overactivity and autonomic dysreflexia. Prospective, large trials are needed to comprehensively evaluate the efficacy and safety of botulinum toxin for this purpose.

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Disclaimer statements

Conflict of interest The authors report no conflicts of interest.

Ethical approval The study was approved by the institution review board (IRB) of Seoul National University Hospital (IRB no.: 1607-176-779).

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